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Total Synthesis

Enantioselective Total Syntheses of (*R*)- and (*S*)-Naphthotectone, and Stereochemical Assignment of the Natural Product

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Abstract: Both isomers of naphthotectone, an isoprenoid quinone from Verbenaceae *Tectona grandis* possessing interesting biological activities, were enantioselectively obtained by two different synthetic routes in which the carbon side-chain of the naphthoquinone core was introduced using either a Sonogashira or a Heck coupling reaction. In both cases, the naphthoquinone core of the final products was obtained by a late-stage anodic treatment. (*R*)-Naphthotectone was obtained in six steps from leuconaphthazarin with an overall yield of 38 % and an enantiomeric excess of 86 %. This compound was found to have the same absolute configuration as the natural product at its C-3′ stereogenic center. (*S*)-Naphthotectone was obtained in five steps from leuconaphthazarin with an overall yield of 36 % and an enantiomeric excess of 80 %.

Introduction

The 1,4-naphthoquinone core is present in many natural products with interesting biological activities.[1] Several examples are shown in Figure 1, and two of these, alkannin and shikonin, play important roles[2] due to their antioxidative, wound-healing, antitumor, antibacterial, antithrombotic, inmunostimulatory, antipyretic, and analgesic activities, amongst others. The vitamin K family, which is important for blood coagulation, is also made up of 1,4-naphthoquinone derivatives. Juglone is a natural occurring dye. As a consequence of all these properties, the search for new molecules that incorporate this important moiety has attracted the attention of numerous research groups around the world.[1]

Naphthotectone (**1**) was recently isolated from teak leaf extracts of *Tectona grandis*, and was identified as one of the main compounds responsible for the allelopathic activity shown by teak, besides being involved in other defense mechanisms.[3] We recently described the first total synthesis of racemic naphthotectone (**1**) from readily available starting materials.[4] The synthetic route was efficient, and involved a late-stage one-pot anodic treatment and demethylation process to form the naphthoquinone core. In this paper, we describe two different enantioselective syntheses of this compound in which the aforementioned strategy is used, with the carbon side-chain of the naphthoquinone core being introduced by Pd coupling reactions (Scheme 1).

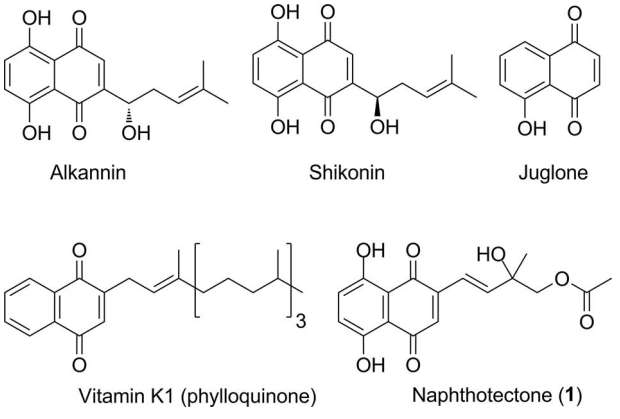

Figure 1. Selected natural products containing the naphthoquinone core.

The first synthetic strategy was designed based on asymmetric dihydroxylation of Weinreb amide[5] **3**, to give the corresponding (*R*)- and (*S*)-3-methylbut-2-yne-3,4-diols **2**.[6] The key point in this strategy was the attachment of the side-chain of the naphthoquinone core using a Sonogashira cross-coupling reaction.[7] The α-hydroxylated double bond was obtained with high *E* selectivity by RedAl [sodium bis(2-methoxyethoxy)aluminum hydride][8] reduction of the α-hydroxyacetylenic intermediate produced by the Sonogashira coupling. Final deprotection and oxidation were carried out by the electrochemical reaction mentioned above.

For the second synthetic strategy, the main difference is that the olefinic side-chain is attached by a Heck-type reaction. This shortens the synthesis by one step, since the reduction reaction is no longer necessary. Furthermore, chiral allylic diol **4** was obtained by a palladium-catalyzed Trost asymmetric allylic alkylation of allylic epoxide **5** using the Trost ligand in a single step.[9]

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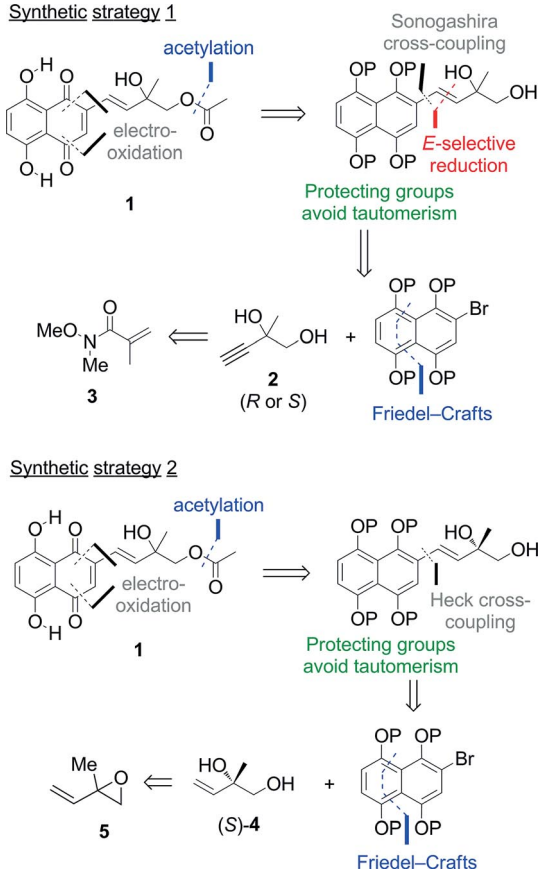
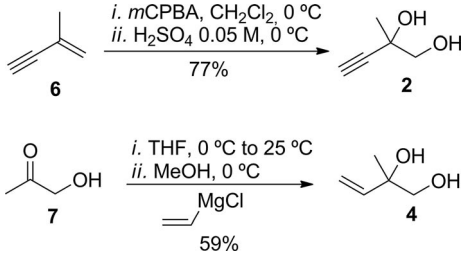


Scheme 1. Retrosynthetic analyses for (*R*)- and (*S*)-naphthotectones (**1**).

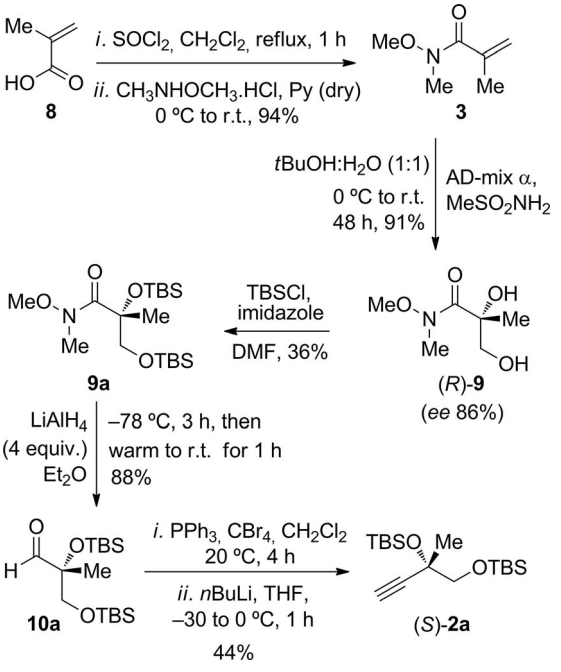
Results and Discussion

Racemic diols **2**[7] and **4**[10] were obtained on a large scale as shown in Scheme 2, and were used to assess the best conditions for the Sonogashira and Heck couplings, respectively.



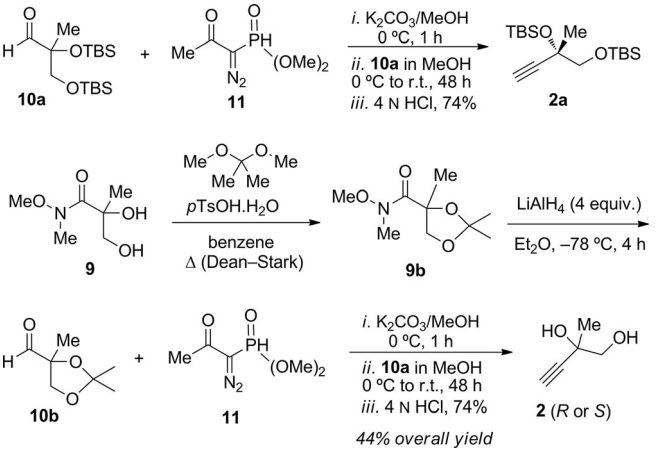
Scheme 2. Syntheses of racemic diols **2** and **4** (*m*CPBA = 3-chloroperbenzoic acid).

Direct access to both enantiomers of acetylenic diol **2** was achieved by Sharpless asymmetric dihydroxylation of enyne **6**. Unfortunately, this reaction yields an almost racemic mixture, as described previously.[6b] In a first approach, the preparation of chiral **2** was accomplished by a previously reported route (Scheme 3).[5a,6] Asymmetric dihydroxylation of Weinreb amide **3** with AD-mix α and β gave diol amide **9** with good *ee* values (86 % *ee* for *R*, and 92 % *ee* for *S*). This reaction was followed by bis-silylation and reduction with lithium aluminum hydride to give aldehyde **10a**. Corey–Fuchs homologation of **10a** gave **2a** in modest yield (44 %).



Scheme 3. Synthesis of chiral alkyne **2a** by Corey–Fuchs reaction of aldehyde **10a** as reported previously[5a,6] (TBS = *tert*-butyldimethylsilyl).

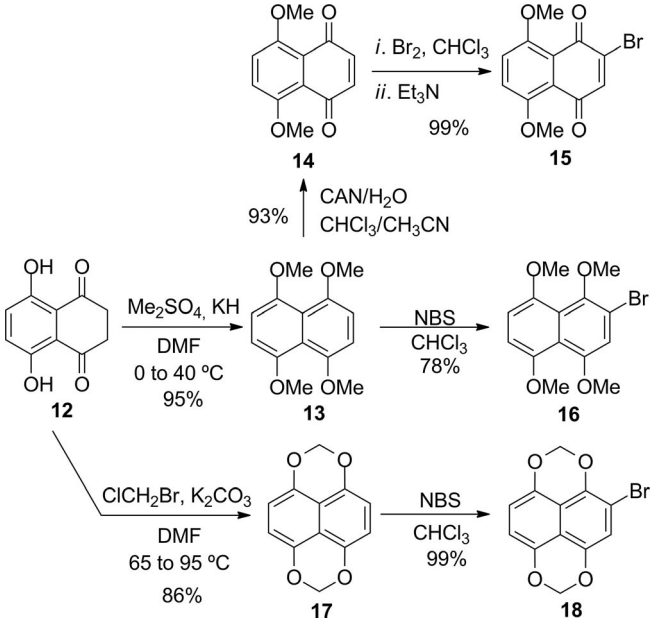
Due to the unexpectedly low yields obtained in the silylation and homologation reactions (the reported yields are 94 and 74 %, respectively),[6b] a different route was developed for the synthesis of diol **2** (Scheme 4). This consisted of Seyferth–Gilbert reaction of aldehyde **10a** with the Bestmann–Ohira reagent (**11**).[11] This approach led to an increase in the yield of **2a** from 44 to 74 %. Better results were also obtained when an acetonide[12] was used as a protecting group for amide **9**. Reduction of amides **9a** and **9b** with lithium aluminum hydride was carried out in dry ethyl ether, because the target aldehyde could not be obtained in dry THF, dichloromethane, or chloroform. Complete reduction required the use of 4 equiv. of $LiAlH_4$ at –78 °C for 4 h. Reduction was not observed when DIBAL (diisobutylaluminium hydride) was used. Thus, diol **2** was obtained in 44 % overall yield from **9** using this new strategy.



Scheme 4. Synthesis of chiral alkyne diol **2** by Seyferth–Gilbert reaction of aldehyde **10b** with the Bestmann–Ohira reagent (**11**).

The enantiomeric excesses of diol **9** (92 % *ee* for *S*, 86 % *ee* for *R*) were determined by formation of the corresponding *O*-methylmandelate esters[13] followed by quantification by NMR spectroscopy (see Supporting Information). Esterification was carried out with the complementary *S* and *R* enantiomers, according to the method proposed by Trost et al.[13b]

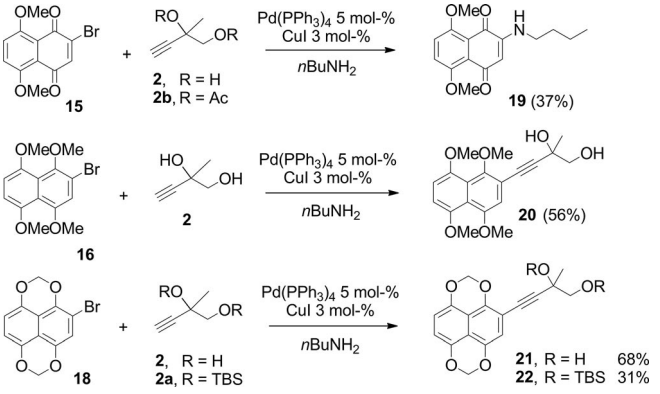
Previously reported procedures were used to prepare three different substrates from **12**[4,14] in order to investigate the Sonogashira coupling with alkyne **2**, as shown in Scheme 5. Vinyl bromide **15** was obtained in excellent yield by permethylation of **12** with dimethyl sulfate, oxidation to the quinone using ceric ammonium nitrate[15] (CAN), and bromination. Aryl bromides **16**[16] and **18**[17] were also prepared in a straightforward manner.



Scheme 5. Preparation of vinyl and aryl bromides **15**, **16**, and **18** for the coupling reactions. NBS = *N*-bromosuccinimide.

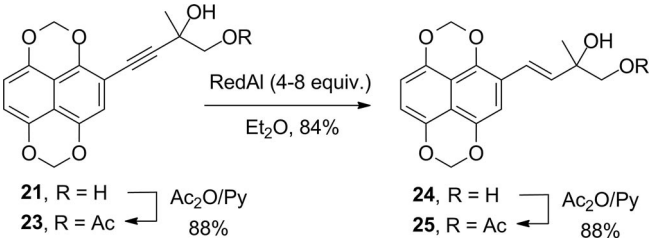
The Sonogashira reaction conditions investigated were similar to those reported previously for the synthesis of speciosins G and P.[7] The coupling of vinyl bromide **15** with diol **2** would lead directly to the naphthoquinone core of the final product. Unfortunately, the desired compound was not detected for any of the conditions we tested. Instead, amine-substituted product **19** was the major product (37 % yield, Scheme 6). This compound proved to be the result of substitution of the bromo substituent by the solvent, *n*-butylamine. Under these conditions, complete cleavage of ester **2b** was also observed, and so this compound was not used further in the synthesis. The couplings of aryl bromides **16** and **18** with racemic diol **2** were more successful, and they gave compounds **20** and **21** in yields of 56 and 68 %, respectively. The reaction with the corresponding racemate of bis-silylated compound **2a**, however, gave **22** in lower yield (31 %).

Reduction of the triple bond of **21** was carried out using Red-Al[8] to give *E*-alkene **24** in high yield (84 %; Scheme 7). A similar reaction was attempted on the monoacetylated derivative of **21** (i.e., **23**). In this case, however, the desired reduction



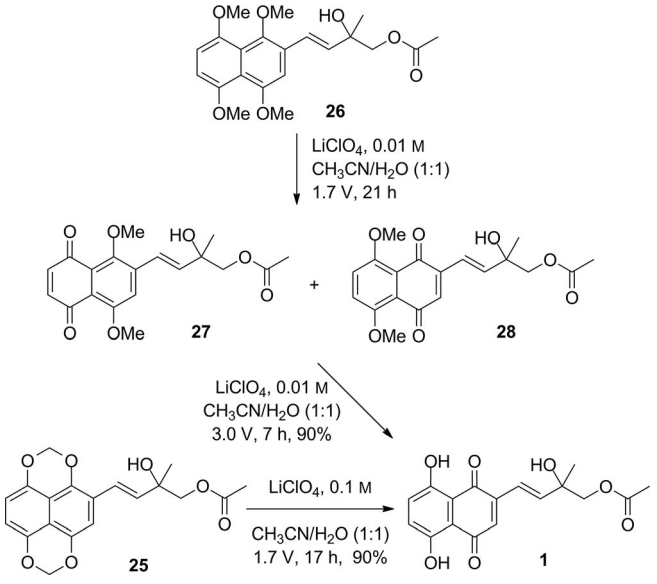
Scheme 6. Sonogashira reaction conditions with racemic diols **2**, **2a**, and **2b**.

was accompanied by reduction of the ester moiety, so further acetylation of the primary alcohol was necessary in both cases. The acetylation was accomplished under standard conditions using acetic anhydride in pyridine.



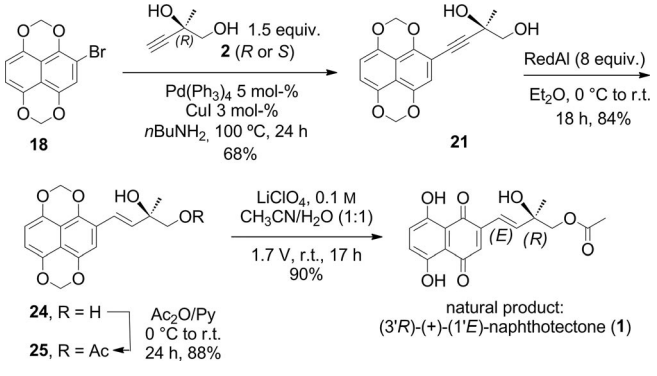
Scheme 7. *E*-selective reduction of the triple bond of **21** with RedAl.

The formation of the quinone moiety from compound **25** by oxidation and deprotection was carried out using anodic treatment. The electrochemical oxidation of organic compounds such as salicylic acid and salicylaldehyde[18] is well known, and has several advantages over typical chemical oxidations. In short, the transformation can be easily controlled, and is a greener and less costly process. The experimental set up was constructed with carbon electrodes under argon, using $LiClO_4$ (0.1 M) in H_2O/CH_3CN (1:1) as the electrolyte (Scheme 8). Interestingly, the reaction proceeded in two steps when methoxy was used as the protecting group (compound **26**). In contrast, when methylenedioxy was used as the protecting group (compound **25**), no evidence of an intermediate was observed by TLC. Both the oxidation and deprotection steps proceed at a constant potential of 1.7 V for 17 h, resulting in clean conversion into naphthotectone in 90 % yield. Thus, the potential difference between the anode and the cathode of the electrical power supply unit was selected as 1700 mV. Naphthotectone (**1**) was easily purified using a Sephadex LH-20 column with isocratic H_2O/CH_3CN mixtures. In a similar procedure reported by Nicolaou and Hepworth[17b] for the synthesis of alkannin and shikonin (see structures in Figure 1), the external voltage was set to 3 V, and the naphthoquinone product was obtained in high yields (80 %) but with only up to 50 % conversion. At higher conversions, side-products began to appear.



Scheme 8. Anodic treatment conditions.

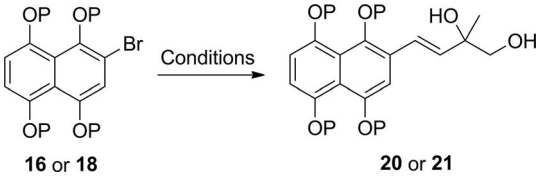
Having established the synthetic route using racemic diol **2**, both enantiomers of naphthotectone could be efficiently accessed as shown in Scheme 9, using either (*R*)- or (*S*)-**2**. Comparison of the optical rotation of the final products with that of the natural product led us to conclude that natural naphthotectone (**1**) has an *R* configuration at the stereogenic center. Thus, the enantioselective total synthesis of the natural product (3′*R*)-(+)-(1′*E*)-naphthotectone (**1**) has been carried out in six steps from leuconaphthazarin (**12**) with an overall yield of 38 % and an enantiomeric excess of 86 %.



Scheme 9. General procedure for the synthesis of (3′*S*)-(–)- and (3′*R*)-(+)-(1′*E*)-naphthotectone (**1**).

A larger amount of the nonnatural *S* isomer of naphthotectone was required to investigate its activity in greater depth, and we therefore developed another synthetic route to this molecule. The route is very similar to the one described above, but uses a Heck coupling to attach the olefinic side-chain, as shown in Table 1. Olefinic diol **4** was readily obtained either in its racemic (Scheme 2)[10] or chiral form through palladium-catalyzed Trost asymmetric allylic alkylation using the *R,R* Trost ligand **30** (Scheme 10).[9] Although higher *ee* (97 %) and yield (91 %) have been reported for diol **4**,[9] in our hands these results could not be reproduced, and an *ee* of 80 % and a yield of 62 % were obtained. Nevertheless, this method does have some advantages over the first approach described above: reduction of the triple bond is no longer required, and chiral olefinic diol **4** can be readily obtained in a single step from commercially available epoxide **29** (Scheme 10). At this point, it is important to note that although only the *S* isomer was obtained in this study, its enantiomer could also be obtained using the *S,S* Trost ligand.

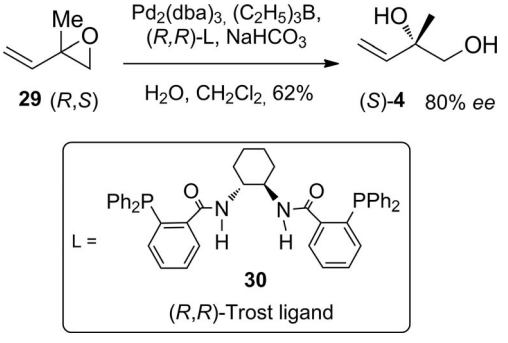
Table 1. Different conditions tested for the Heck cross-coupling reaction of aryl halides **16** and **18** and racemic allylic diol **4** [dppp = 1,3-bis(diphenylphosphino)propane].



16 or **18** **20** or **21**

RBr	Pd source	Phosphine	Base	Solvent	Yield [%]
18	$Pd(OAc)_2$ (0.3 equiv.)	P(*o*-Tol)$_3$ (0.4 equiv.)	Et_3N	toluene 72 h	60
18	$PdCl_2(PPh_3)_2$ (0.2 equiv.)	dppp (0.2 equiv.)	$NaHCO_3$	toluene 72 h	n.r.[a]
18	$Pd(OAc)_2$ (0.3 equiv.)	–	Et_4NBr NaOAc	CH_3CN 71 h	n.r.
16	$Pd(OAc)_2$ (0.3 equiv.)	P(*o*-Tol)$_3$ (0.4 equiv.)	Et_3N	toluene 72 h	n.r.
16	$PdCl_2(PPh_3)_2$ (0.2 equiv.)	dppp (0.2 equiv.)	Et_3N	DMF 72 h	n.r.
16	$Pd(PPh_3)_4$ (0.2 equiv.)	–	Et_3N	toluene 72 h	n.r.

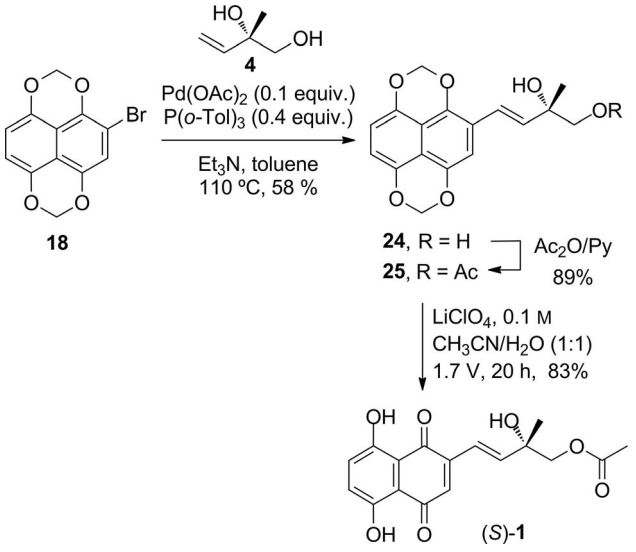
[a] n.r.: no reaction took place, and the starting material was recovered.



Scheme 10. Synthesis of chiral diol **4** (dba = dibenzylideneacetone).

Racemic diol **4** was used to test the Heck reaction with aryl bromides **16** and **18**, and the conditions are given in Table 1. The only conditions that led to product formation involved the use of $Pd(OAc)_2$ as Pd source, P(*o*-Tol)$_3$, Et_3N as base, and toluene as solvent (Table 1, entry 1). Under these conditions, the coupling product was obtained in 60 % yield.

The optimized conditions described above were used to obtain chiral **24** in 58 % yield. The final steps for the synthesis of (*S*)-naphthotectone are shown in Scheme 11.



Scheme 11. Final steps in the synthesis of (*S*)-naphthotectone.

Conclusions

In summary, (*R*)- and (*S*)-naphthotectones were obtained by two different and convergent synthetic routes, using as key steps Pd-catalyzed cross-coupling reactions (Sonogashira and Heck), and a late-stage one-pot anodic oxidation and demethylation process. The absolute configuration of the natural product was assigned as *R* by comparison of the optical rotations of the chiral synthetic compounds obtained with that of the natural product. Biochemical tests are being carried out on both isomers of naphthotectone, and the results will be published in due course.

Experimental Section

General Remarks: IR spectra (KBr) were recorded with an FTIR spectrometer, and are given as wavenumbers of absorption (cm^{-1}). Only selected IR absorption bands are reported. NMR spectra were recorded with 400 and 500 MHz spectrometers. Chemical shifts are given in ppm; ^1H spectra were calibrated using residual ^1H signals of $CDCl_3$ (δ = 7.26 ppm), and ^{13}C spectra were also referenced to the $CDCl_3$ solvent signal (δ = 77.0 ppm). HRMS was carried out with a MicrOTOF-Q-I mass spectrometer (70 eV). HPLC was carried out using an instrument with refractive index (RI) detection, using Merck LiChrospher columns: SI 60 (5 μm, 250 × 4 mm). Melting points were recorded with a melting-point apparatus. Commercially available reagents and solvents were analytical grade, or were purified by standard procedures before use. Compounds were analyzed by IR spectroscopy, ^1H and ^{13}C NMR spectroscopy, and high resolution ESI mass spectrometry, and the data are consistent with the proposed structures.

General Procedure for the Sonogashira Coupling:[7] Aryl halide **15**, **16**, or **18** (2.5 mmol) and *n*-butylamine (6.4 mL) were put into a flame-dried round-bottomed flask under an argon atmosphere. A mixture of terminal alkyne **2** (1–1.5 equiv.), $Pd(PPh_3)_4$ (5 or 3 mol-%), and CuI (3 mol-%) in *n*-butylamine (30 mL) was added. The mixture was heated for 24 h at 100 °C, and then it was poured into H_2O (80 mL). The mixture was extracted with ethyl acetate (3 × 80 mL). The combined organic layers were washed with brine, dried with anhydrous Na_2SO_4, and evaporated under reduced pressure. The crude material was purified by silica gel column chromatography, eluting with mixtures of ethyl acetate/hexane, 10–50 %.

2-(Butylamino)-5,8-dimethoxynaphthalene-1,4-dione (19): Equimolar amounts of aryl halide **15** and alkyne **2** reacted in $nBuNH_2$ in the presence of $Pd(PPh_3)_4$ (5 mol-%) and CuI (3 mol-%). The Sonogashira coupling product was not observed. The crude material was purified on a Sephadex LH-20 column eluting with dichloromethane/hexanes, 19:1 to give **19** (18.0 mg, 37 %) as an amorphous orange solid. R_f = 0.36 (50 % EtOAc in hexane, stain: oleum). IR (neat): $\tilde{\nu}$ = 3361, 2957, 1617, 1256, 1203 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.33 (d, *J* = 9.5 Hz, 1 H), 7.17 (d, *J* = 9.5 Hz, 1 H), 5.68 (s, 1 H), 5.60 (s, 1 H), 3.95 (s, 3 H), 3.93 (s, 3 H), 3.07–3.15 (m, 2 H), 1.63 (qt, *J* = 7.5, Hz, 2 H), 1.42 (st, *J* = 7.5, Hz, 2 H), 0.94 (t, *J* = 7.5 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 183.7, 181.3, 154.7, 153.4, 147.4, 123.0, 122.5, 120.0, 117.9, 101.8, 57.5, 56.8, 42.3, 30.5, 20.3, 13.8 ppm. HRMS (ESI-TOF): calcd. for $C_{16}H_{19}O_4N$ $[M + H]^+$ 290.1416; found 290.1392.

2-Methyl-4-(1,4,5,8-tetramethoxynaphthalene-2-yl)but-3-yne-1,2-diol (20): Aryl halide **16** and alkyne **2** (1.5 equiv.) reacted in $nBuNH_2$ in the presence of $Pd(PPh_3)_4$ (5 mol-%) and CuI (3 mol-%). The crude material was purified by silica gel column chromatography, eluting first with EtOAc in hexanes (20 %) to recover the unreacted starting material, 2-bromo-1,4,5,8-tetramethoxynaphthalene (**16**), and then with EtOAc in hexane (80 %) to give **20** (56 %). R_f = 0.125 (50 % EtOAc in hexane, stain: oleum). IR (neat): $\tilde{\nu}$ = 3408, 2917, 1606 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 6.87 (d, *J* = 8.8 Hz, 1 H), 6.85 (d, *J* = 8.8 Hz, 1 H), 6.80 (s, 1 H), 3.93 (s, 3 H), 3.91 (s, 3 H), 3.89 (s, 3 H), 3.87 (s, 3 H), 3.80 (d, *J* = 11.0 Hz, 1 H), 3.61 (d, *J* = 11.0 Hz, 1 H), 1.60 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 153.1, 152.8, 151.5, 150.5, 122.9, 120.9, 109.8, 25.2, 109.6, 108.6, 94.8, 81.8, 71.2, 69.6, 62.3, 58.0, 57.3, 57.1 ppm. HRMS (ESI-TOF): calcd. for $C_{19}H_{22}O_6Na$ $[M + Na]^+$ 369.1469; found 369.1471.

2-Methyl-4-[1,8:4,5-bis(methylenedioxy)naphthalene-2-yl]but-3-yne-1,2-diol (21): Aryl halide **18** and racemic alkyne **2** (1.5 equiv.) reacted in $nBuNH_2$ in the presence of $Pd(PPh_3)_4$ (5 mol-%) and CuI (3 mol-%). The crude material was purified by silica gel column chromatography, eluting first with EtOAc in hexane (20 %) to recover the unreacted starting material **18**, and then with EtOAc in hexane (80 %) to give **21** (68 %). R_f = 0.19 (50 % EtOAc in hexane, stain: oleum), m.p. 135–136 °C. IR (neat): $\tilde{\nu}$ = 3377, 1621 cm^{-1}. ^1H NMR (400 MHz, CD_3OD): δ = 6.85 (s, 2 H), 6.81 (s, 1 H), 5.53 (s, 2 H), 5.48 (s, 2 H), 3.63 (d, *J* = 11.0 Hz, 1 H), 3.60 (d, *J* = 11.0 Hz, 1 H), 1.54 (s, 3 H) ppm. ^{13}C NMR (100 MHz, CD_3OD): δ = 147.4, 145.9, 145.6, 145.3, 116.0, 115.9, 111.9, 110.9, 110.7, 104.9, 98.4, 93.2, 93.2, 79.3, 71.1, 69.7, 26.2 ppm. HRMS (ESI-TOF): calcd. for $C_{17}H_{13}O_5$ $[M + H - H_2O]^+$ 297.0767; found 297.0763.

(*R*)- and (*S*)-2-Methyl-4-[1,8:4,5-bis(methylenedioxy)naphthalene-2-yl]but-3-yne-1,2-diol (21): Obtained from 2-bromo-1,8:4,5-bis(methylenedioxy)naphthalene (**18**; 85.0 mg, 0.29 mmol) and (3*R*)- or (3*S*)-3-methylbut-2-yne-3,4-diol (**2**; 43.2 mg, 0.43 mmol, 1.5 equiv.) following the procedure described for racemic **21**. Compound (*R*)-**21** (61.4 mg, 68 %); $[\alpha]_D^{25}$ = +12.6 (*c* = 0.01, MeOH). Compound (*S*)-**21** (60.0 mg, 67 %); $[\alpha]_D^{25}$ = –12.0 (*c* = 0.01, MeOH).

2,2,3,3,5,8,8,9,9-Nonamethyl-5-{[1,8:4,5-bis(methylenedioxy)naphthalen-2-yl]ethynyl}-4,7-dioxa-3,8-disiladecane (22): Aryl halide **18** and racemic alkyne **2a** (1.5 equiv.) reacted in $nBuNH_2$ in the presence of $Pd(PPh_3)_4$ (5 mol-%) and CuI (3 mol-%). The crude material was purified by HPLC eluting first with EtOAc in hexane (3 %) to give unreacted starting material **18** (retention time: 10 min), and then **22** (retention time: 13 min; 31 %) as a colorless

amorphous solid. R_f = 0.75 (10 % EtOAc in hexane, stain: oleum). IR (neat): $\tilde{\nu}$ = 1605, 1129 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.85 (s, 2 H), 6.82 (s, 1 H), 5.52 (s, 2 H), 5.50 (s, 2 H), 3.67 (d, J = 9.4 Hz, 1 H), 3.56 (d, J = 9.4 Hz, 1 H), 1.54 (s, 3 H), 0.92 (s, 9 H), 0.89 (s, 9 H), 0.24 (s, 3 H), 0.23 (s, 3 H), 0.10 (s, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.3, 144.6, 144.4, 143.9, 114.9, 114.9, 111.3, 109.9, 109.6, 104.3, 98.6, 91.9, 91.8, 79.3, 71.9, 70.8, 27.8, 26.0, 25.9, 18.5, 18.2, –2.8, –2.9, –5.2 ppm.

2-Hydroxy-2-methyl-4-[1,8:4,5-bis(methylenedioxy)naphthalene-2-yl]but-3-ynyl Acetate (23): Acetic anhydride (35.1 μL, 0.32 mmol) was added to a stirred and cooled solution (0 °C) of 2-methyl-4-[1,8:4,5-bis(methylenedioxy)naphthalene-2-yl]but-3-yne-1,2-diol (**21**; 100.0 mg, 0.33 mmol) in dry pyridine (900 μL). The mixture was stirred for 18 h, and then it was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluting with EtOAc in hexane (50 %), to give **23** (99.7 mg, 88 %) as a colorless amorphous solid. R_f = 0.43 (50 % EtOAc in hexane, stain: oleum). IR (neat): $\tilde{\nu}$ = 3448, 2223, 1742, 1621 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 6.85 (s, 2 H), 6.80 (s, 1 H), 5.54 (s, 2 H), 5.48 (s, 2 H), 4.40 (d, J = 11.1 Hz, 1 H), 4.14 (d, J = 11.1 Hz, 1 H), 2.16 (s, 3 H), 1.63 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.0, 146.5, 144.6, 144.3, 143.9, 115.1, 114.7, 111.1, 110.3, 109.9, 103.1, 95.3, 92.0, 91.9, 79.4, 71.1, 67.7, 26.1, 21.0 ppm. HRMS (ESI-TOF): calcd. for $C_{19}H_{15}O_6$ $[M + H - H_2O]^+$ 339.0874; found 339.0869.

(3*E*)-2-Methyl-4-[1,8:4,5-bis(methylenedioxy)naphthalen-2-yl]but-3-ene-1,2-diol (24)

Method A, *trans*-Selective Reduction: A solution of sodium bis(2-methoxyethoxy)aluminum hydride (RedAl; 3.5 M in toluene; 64.1 μL, 0.22 mmol, 4 equiv.) was put into a flame-dried round-bottomed flask under an argon atmosphere, and then anhydrous Et_2O (3 mL) was added. The mixture was cooled to 0 °C, and a solution of 2-hydroxy-2-methyl-4-[1,8:4,5-bis(methylenedioxy)naphthalene-2-yl]but-3-ynyl acetate (**23**; 20.0 mg, 0.056 mmol) in dry Et_2O (3 mL) was added dropwise. After the addition was complete (10 min), the ice bath was removed, and the reaction mixture was allowed to warm up to room temperature. Once the mixture had reached room temperature, a yellowish solution had formed, and TLC indicated that the starting material had been consumed. The reaction mixture was then cooled to 0 °C, and quenched by the addition of $Na_2S_2O_3$ (10 % aq.; 10 mL), and then the mixture was stirred for 30 min. Saturated aqueous NH_4Cl (10 mL) was added, and the mixture was stirred for an additional 40 min. The mixture was extracted with ethyl acetate (4 × 50 mL), and the combined organic layers were washed with brine, dried with anhydrous Na_2SO_4, and evaporated under reduced pressure. The crude material was purified by silica gel column chromatography, eluting with EtOAc in hexane (60 %) to give **24** (14.4 mg, 81 %). R_f = 0.25 (50 % EtOAc in hexane, stain: oleum). IR (neat): $\tilde{\nu}$ = 3444, 3023, 2898, 1687, 1641, 1610 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.41 (s, 3 H), 3.56 (d, J = 11.0 Hz, 1 H), 3.64 (d, J = 11.0 Hz, 1 H), 5.49 (s, 2 H), 5.52 (s, 2 H), 6.32 (d, J = 16.3 Hz, 1 H), 6.79 (d, J = 8.2 Hz, 1 H), 6.83 (d, J = 8.2 Hz, 1 H), 6.98 (s, 1 H), 7.07 (d, J = 16.3 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.8, 144.7, 144.6, 141.6, 134.8, 122.1, 117.9, 115.4, 114.7, 109.5, 109.1, 105.8, 91.9, 91.8, 73.9, 70.1, 24.6 ppm. HRMS (ESI-TOF): calcd. for $C_{17}H_{15}O_5$ $[M + H - H_2O]^+$ 299.0919; found 299.0922.

Method B, *trans*-Selective Reduction: A solution of sodium bis(2-methoxyethoxy)aluminum hydride (RedAl; 3.5 M in toluene; 637 μL, 2.23 mmol, 7 equiv.) was put into a flame-dried round-bottomed flask under an argon atmosphere, and then anhydrous Et_2O (30 mL) was added. The solution was cooled to 0 °C (ice bath), and powdered 2-methyl-4-[1,8:4,5-bis(methylenedioxy)naphthalene-2-yl]but-3-yne-1,2-diol (**21**; 100.0 mg, 0.32 mmol) was added (*Note:* this compound is not soluble in Et_2O). After the addition was complete, the ice bath was removed, and the reaction mixture was allowed to warm to room temperature. The resulting emulsion was stirred for 5 h to give a yellowish solution. After this time, TLC indicated that the starting material had been consumed. The reaction mixture was cooled to 0 °C, then it was quenched by the addition of $Na_2S_2O_3$ (10 % aq; 50 mL), and the mixture was stirred for 30 min. Saturated aqueous NH_4Cl (50 mL) was added to the mixture, and stirring was continued for an additional 40 min. The product was extracted with ethyl acetate (4 × 100 mL), and the combined organic layers were washed with brine, dried with anhydrous Na_2SO_4, and evaporated under reduced pressure. The crude material was purified by silica gel column chromatography, eluting with EtOAc in hexane (40 %) to give **24** (85.3 mg, 84 %).

Method C, Heck Coupling:[19] $Pd(OAc)_2$ (5.2 mg, 0.023 mmol), P(*o*-Tol)$_3$ (28.0 mg, 0.092 mmol), Et_3N (0.93 mL, 2.4 mmol), and 2-bromo-1,8:4,5-bis(methylenedioxy)naphthalene (**18**; 45.7 mg, 0.155 mmol) were added to a flame-dried flask containing dry toluene (3 mL) under a nitrogen atmosphere. The flask was then placed under reduced pressure for 10 s, and refilled with argon; the mixture was stirred for 15 min, and then 2-(*S*)-2-methyl-but-3-ene-1,2-diol (**4**; 12.0 mg, 0.103 mmol) was added. The mixture was heated at 110 °C. The solution was initially a clear amber color, but it gradually darkened, and palladium precipitated. After 12 h, another portion of $Pd(OAc)_2$ (0.1 equiv.) was added. This operation was repeated three times. During this period of time, the stirring was kept slow to avoid palladium precipitation. The reaction was monitored by TLC, and after the starting material had been consumed, the heat source was removed. Methanol (5 mL) was added when the reaction mixture had reached room temperature. The mixture was filtered under vacuum on a neutral Celite® pad to remove the palladium. The pad was washed with methanol (2 × 20 mL), and the combined organic phases were concentrated under vacuum. The product was purified by silica gel column chromatography, eluting with EtOAc in hexane (50 %), to give **24** as a pale yellow oil. R_f = 0.3 (40 % EtOAc in hexane).

(2*R*)- and (2*S*)-(3*E*)-2-Methyl-4-[1,8:4,5-bis(methylenedioxy)-2-naphthyl]but-3-ene-1,2-diol [(*R*)-24 and (*S*)-24]: Obtained from (3*R*)-2-methyl-4-[1,8:4,5-bis(methylenedioxy)naphthalene-2-yl]but-3-yne-1,2-diol [(*R*)-**21**] or (3*S*)-2-methyl-4-[1,8:4,5-bis(methylenedioxy)naphthalene-2-yl]but-3-yne-1,2-diol [(*S*)-**21**] using the procedure described above for racemic **24**. Compound (*R*)-**24** (100.0 mg, 0.32 mmol, 84 %); $[\alpha]_D^{20}$ = +19.5 (c = 0.01, MeOH). Compound (*S*)-**24** (100.0 mg, 0.32 mmol, 84 %); $[\alpha]_D^{20}$ = –19.0 (c = 0.01, MeOH).

(3*E*)-2-Hydroxy-2-methyl-4-[1,8:4,5-bis(methylenedioxy)-2-naphthyl]but-3-enyl Acetate (25): Acetic anhydride (35 μL, 0.32 mmol) was added to a stirred and cooled solution (0 °C) of (3*E*)-2-methyl-4-[1,8:4,5-bis(methylenedioxy)naphthalen-2-yl]but-3-ene-1,2-diol (**24**; 100.0 mg, 0.32 mmol) in dry pyridine (2 mL). The mixture was stirred for 18 h, and then it was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluting with EtOAc in hexane (50 %), to give **25** (99.6 mg, 88 %) as a pale pink amorphous solid. R_f = 0.41 (50 % EtOAc in hexane, stain: oleum), m.p. 128 °C. IR (neat): $\tilde{\nu}$ = 3422, 2924, 1739, 1603 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.07 (d, J = 16.2 Hz, 1 H), 6.96 (s, 1 H), 6.82 (d, J = 8.2 Hz, 1 H), 6.79 (d, J = 8.2 Hz, 1 H), 6.31 (d, J = 16.2 Hz, 1 H), 5.52 (s, 2 H), 5.49 (s, 2 H), 4.20 (d, J = 11.2 Hz, 1 H), 4.08 (d, J = 11.2 Hz, 1 H), 2.10 (s, 3 H), 1.43 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.2, 144.8, 144.7, 144.5, 141.6, 134.1, 122.0, 117.8, 115.4, 114.7, 109.5, 109.1, 105.7, 91.9, 91.7, 72.7, 71.1, 25.2, 21.0 ppm. HRMS (ESI-TOF): calcd. for $C_{19}H_{17}O_6$ $[M + H - H_2O]^+$ 341.1029; found 341.1025.

(*R*)- and (*S*)-(3*E*)-2-Hydroxy-2-methyl-4-[1,8:4,5-bis(methylenedioxy)-2-naphthyl]but-3-enyl Acetate [(*R*)-25 and (*S*)-25]: Obtained from (*R*)-(3*E*)-2-methyl-4-[1,8:4,5-bis(methylenedioxy)-naphthalen-2-yl]but-3-ene-1,2-diol [(*R*)-**24**] and (*S*)-(3*E*)-2-methyl-4-[1,8:4,5-bis(methylenedioxy)naphthalen-2-yl]but-3-ene-1,2-diol [(*S*)-**24**] (100.0 mg, 0.32 mmol) following the procedure described for racemic **25**. Compound (*R*)-**25** (88 %); $[\alpha]_D^{20}$ = +22.6 (*c* = 0.01, MeOH). Compound (*S*)-**25** (88 %); $[\alpha]_D^{20}$ = –20.0 (*c* = 0.01, MeOH).

Naphthotectone (1): Anodic treatment: a solution of racemic (3*E*)-2-hydroxy-2-methyl-4-[1,8:4,5-bis(methylenedioxy)-2-naphthyl]but-3-enyl acetate (**25**; 20.0 mg, 0.056 mmol) and lithium perchlorate (167.1 mg, 1.57 mmol) in acetonitrile (50 % aq.; 15.7 mL) was introduced under an argon atmosphere into an undivided electrolytic cell with carbon electrodes. (For details, see Supporting Information) The solution was electrolyzed at 1.71 V for 17 h to generate the desired naphthotectone. The solvent was removed under reduced pressure at 45 °C to a volume of 5 mL, and the resulting solution was extracted with chloroform (6 × 10 mL). The organic layer was washed with brine, and dried with anhydrous Na_2SO_4. The solvent was removed, and the residue was purified on Sephadex LH-20, eluting with acetonitrile in water (60 %) to give analytically pure naphthotectone (**1**; 16.7 mg, 90 %) as an amorphous red solid. R_f = 0.25 (60 % acetonitrile in water). The spectroscopic data are in good agreement with those previously reported for the natural product.[3] HRMS (ESI-TOF): calcd. for $C_{17}H_{16}O_7Na$ $[M + Na]^+$ 355.0805; found 355.0794.

(3′*R*)-(1′*E*)-Naphthotectone (1): Obtained from (*R*)-(3*E*)-2-hydroxy-2-methyl-4-[1,8:4,5-bis(methylenedioxy)-2-naphthyl]but-3-enyl acetate [(*R*)-**25**; 20.0 mg, 0.32 mmol] following the procedure described above for racemic **1** (90 %). $[\alpha]_D^{20}$ = +83.3 (*c* = 0.003, $CHCl_3$).

(3′*S*)-(1′*E*)-Naphthotectone (1): Obtained from (*S*)-(3*E*)-2-hydroxy-2-methyl-4-[1,8:4,5-bis(methylenedioxy)-2-naphthyl]but-3-enyl acetate [(*S*)-**25**; 20.0 mg, 0.32 mmol] following the procedure described for racemic **1** (90 %). $[\alpha]_D^{20}$ = –87.5 (*c* = 0.004, $CHCl_3$).

Supporting Information: Experimental conditions for known compounds, and ^1H and ^{13}C NMR spectra of most representative compounds.

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[1] a) L. I. L. López, S. D. N. Flores, S. Y. S. Belmares, A. S. Galindo, *Vitae Rev. Fac. Quím. Farm.* **2014**, *21*, 248–258; b) P. Babula, V. Adam, L. Havel, R. Kizek, *Curr. Pharm. Anal.* **2009**, *5*, 47–68; c) L.-O. Klotz, X. Hou, C. Jacob, *Molecules* **2014**, *19*, 14902–14918.
[2] V. P. Papageorgiou, A. N. Assimopoulou, E. A. Couladouros, D. Hepworth, K. C. Nicolaou, *Angew. Chem. Int. Ed.* **1999**, *38*, 270–300; *Angew. Chem.* **1999**, *111*, 280–311.
[3] R. Lacret, R. Varela, J. G. Molinillo, C. Nogueiras, F. Macías, *J. Chem. Ecol.* **2011**, *37*, 1341–1348.
[4] G. A. Guerrero-Vásquez, C. K. Z. Andrade, J. M. G. Molinillo, F. A. Macías, *Eur. J. Org. Chem.* **2013**, 6175–6180.
[5] a) S. Nahm, S. M. Weinreb, *Tetrahedron Lett.* **1981**, *22*, 3815–3818; b) N. D. Smith, M. Goodman, *Org. Lett.* **2003**, *5*, 1035–1037.
[6] a) Y. L. Bennani, K. B. Sharpless, *Tetrahedron Lett.* **1993**, *34*, 2079–2082; b) D. W. Knight, X. Qing, *Tetrahedron Lett.* **2009**, *50*, 3534–3537; c) A. Avenoza, J. H. Busto, F. Corzana, G. Jimenez-Oses, J. M. Peregrina, *Chem. Commun.* **2004**, 980–981; d) A. Avenoza, C. Cativiela, J. M. Peregrina, D. Sucunza, M. A. M. Zurbano, *Tetrahedron: Asymmetry* **2001**, *12*, 1383–1388; e) T. Kusakabe, Y. Kawai, K. Kato, *Org. Lett.* **2013**, *15*, 5102–5105.
[7] G. A. Guerrero-Vásquez, N. Chinchilla, J. M. G. Molinillo, F. A. Macías, *J. Nat. Prod.* **2014**, *77*, 2029–2036.
[8] a) S. E. Denmark, T. K. Jones, *J. Org. Chem.* **1982**, *47*, 4595–4597; b) C. T. Meta, K. Koide, *Org. Lett.* **2004**, *6*, 1785–1787.
[9] B. M. Trost, E. J. McEachern, *J. Am. Chem. Soc.* **1999**, *121*, 8649–8650.
[10] J. S. Arnold, H. M. Nguyen, *J. Am. Chem. Soc.* **2012**, *134*, 8380–8383.
[11] a) H. D. Dickson, S. C. Smith, K. W. Hinkle, *Tetrahedron Lett.* **2004**, *45*, 5597–5599; b) A. Sathish Reddy, P. Gangadhar, P. Srihari, *Tetrahedron: Asymmetry* **2013**, *24*, 1524–1530; c) D. F. Taber, S. Bai, P.-F. Guo, *Tetrahedron Lett.* **2008**, *49*, 6904–6906.
[12] M. Ostovar, C. M. Marson, *Tetrahedron* **2013**, *69*, 6639–6647.
[13] a) D. Bellus, R. Brown, J. Clayden, L. Cox, J. Eames, L. Fader, P. Forgione, C. Frost, F. Greaney, D. M. Hodgson, *Science of Synthesis: Houben-Weyl Methods of Molecular Transformations*, vol. 36: *Alcohols*, Thieme, Stuttgart, Germany, **2014**; b) B. M. Trost, J. L. Belletire, S. Godleski, P. G. McDougal, J. M. Balkovec, J. J. Baldwin, M. E. Christy, G. S. Ponticello, S. L. Varga, J. P. Springer, *J. Org. Chem.* **1986**, *51*, 2370–2374.
[14] a) D. B. Bruce, R. H. Thomson, *J. Chem. Soc.* **1955**, 1089–1096 (resumed); b) B. Horowska, Z. Mazerska, A. Ledochowski, G. Cristalli, P. Franchetti, S. Martelli, *Eur. J. Med. Chem.* **1988**, *23*, 91–96; c) L.-J. Huang, F.-C. Chang, K.-H. Lee, J.-P. Wang, C.-M. Teng, S.-C. Kuo, *Bioorg. Med. Chem.* **1998**, *6*, 2261–2269; d) R. Huot, P. Brassard, *Can. J. Chem.* **1974**, *52*, 838–842; e) J. R. Lewis, J. Paul, *Z. Naturforsch. B* **1977**, *32*, 1473–1475.
[15] D.-F. Xu, P.-J. Guan, S.-S. Li, *J. Chem. Res.* **2006**, 779–780.
[16] M. Kawasaki, F. Matsuda, S. Terashima, *Tetrahedron* **1988**, *44*, 5713–5725.
[17] a) J. L. Bloomer, W. Zheng, *Synth. Commun.* **1998**, *28*, 2087–2095; b) K. C. Nicolaou, D. Hepworth, *Angew. Chem. Int. Ed.* **1998**, *37*, 839–841; *Angew. Chem.* **1998**, *110*, 864–866; c) A.-H. Zhao, D.-F. Xu, W. Zhuo, Z. Rao, S.-S. Li, *J. Chem. Res.* **2007**, 647–648.
[18] N. Matyasovszky, M. Tian, A. Chen, *J. Phys. Chem. A* **2009**, *113*, 9348–9353.
[19] F. Löbermann, L. Weisheit, D. Trauner, *Org. Lett.* **2013**, *15*, 4324–4326.

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